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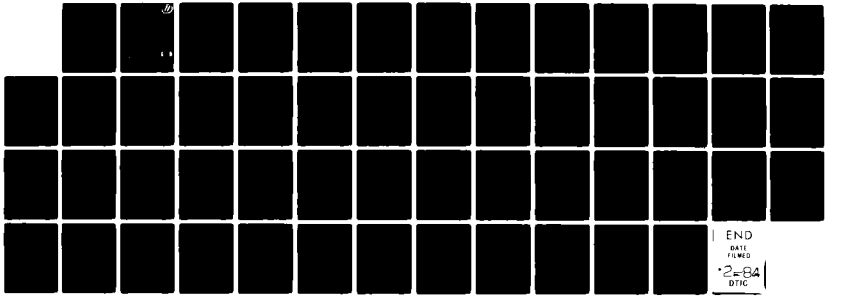

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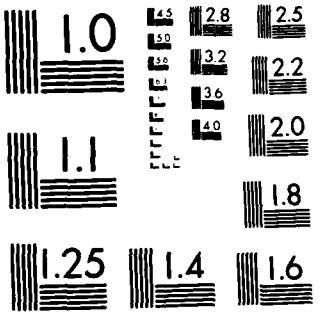

Report No. 821

AD

Investigation of Visual Performance after Administration of Cholinergic Blocking Agents

II. Atropine

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Roy Baker, O.D.
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Arthur Jampolsky, M.D.

April 1982

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U.S. Army Medical Research and Development Command
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Contract No. DAMD 17-80-C-0066

Optical Sciences Group, Inc.
(Visual Sciences Division)
1331 Commerce Street
Petaluma, California 94952

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Atropine is commonly used in anesthesiology and in ophthalmology. It is one of the effective agents for blocking the action of organophosphate nerve agents. Since soldiers in the field are issued atropine auto-injector syringes for use in event of exposture to organophosphates, there is a possiblity that the drug will be injected in the absence of the organophosphate agent. Under these circumstances, are there any effects on vision or vision performance which would render soldiers unable to perform at maximum efficiency?

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20. Abstract (Continued)

We performed two experiments testing the effects of 2 milligrams of atropine per 70 kilograms of body weight and placebo on general vision functions and on some more applied vision tests. In both of these experiments, atropine produced an increase in pulse rate 90 minutes after injection. This increased pulse rate had returned to normal 4-1/2 hours after injection. Subjects reported feeling "high" or intoxicated, and they reported dry mouth and dry skin during this same period. At the end of the experimental period, these sensations had returned to normal.

In our first experiment, we used 10 subjects, aged from 20 to 33 years. We tested amplitude of accommodation, dynamics of accommodation, heterophoria, pupil dynamics, static visual acuity, refractive state, contrast sensitivity function, glare recovery, intraocular pressure, depth perception, saccadic eye movements and postural stability. Atropine reduced the amplitude of accommodation by 1-2 diopters and increased pupil size for periods beyond 4 hours after the injection. These effects were statistically significant, but had either small impact or no effect on the other measured vision functions. Contrast sensitivity showed a slight reduction 240 minutes after drug injection and the time constant of the glare recovery function appeared prolonged after atropine.

In our second experiment involving 6 subjects, (aged from 21 to 32 years), we examined the effects of atropine on a visual search task, which was conducted while the subject was seated in a moving chair. The chair was rotated with a sinusoidal wave form with a frequency of 1Hz over an amplitude of approximately 5 degrees. The search task had oculomoter, visual gross motor and short-term memory components. It was comparable in complexity to many tasks performed in military environments. We found no effect of the drug on search performance or on the manual control skills necessary to perform the task. In a second task, we measured the time taken for subjects to repeatedly change their accommodative state from near to far and identify targets presented at optical infinity and at 40 centimeters. Subjects were able to perform this task as rapidly and as accurately after atropine as before the drug.

We conclude that atropine at 2 milligrams per 70 kilograms of body weight will have little effect on those vision functions which influence general performance. There may however be military situations in which heat stress and psychological stress combine to accentuate the effects of atropine and have a detrimental effect on performance.

FOREWORD

This Final Report was written for the U.S. Army Medical Research and Development Command by the investigators of a study supported by a U.S. Army Contract (No. DAMD 17-80-C-0066). This contract was awarded to the Visual Sciences Division of Optical Sciences Group, Inc., Petaluma, California, which directed, guided, and administered the research study. The experimental phases of the study were conducted at the Smith Kettlewell Institute of Visual Sciences at the Pacific Medical Center in San Francisco. We gratefully acknowledge the space, facilities, and services provided by the institute.

We are grateful to Catherine Carver, who provided administrative and secretarial services essential to the conduct of the experiment. We would also like to acknowledge the assistance provided by Peter Shelley, M.D., and Marc Cruciger, M.D. in conducting these experiments. We thank our subjects, who must remain anonymous, for cheerfully and patiently enduring many hours of testing.

For the protection of human subjects the investigators have adhered to the policies of applicable Federal law 45FR46.

Citation of trade names in this report does not constitute an official Department of the Army endorsement or approval of the use of such items.

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INTRODUCTION

Atropine is probably the best known and most widely used of the cholinergic blocking agents. It is used in ophthalmology and anesthesiology, and is also used as an antidote to poisoning by organophosphate compounds. These chemicals are extensively used as pesticides and as possible chemical warfare agents.

The organophosphates deactivate acetylcholinesterase, the enzyme which is necessary to break down acetylcholine and to produce the (appropriately) short lived consequences of neural discharges at the neuromuscular junction and other neural transmission sites. When acetylcholinesterase is deactivated, acetylcholine accumulates at the nerve endings and produces (in severe cases) respiratory distress, gastrointestinal symptoms, convulsions, and death. Atropine simply blocks the action of acetylcholine, and thus reduces the consequences of its accumulation at nerve endings.

In the military context, there is great concern over the effects of drugs such as atropine when they are administered as antidotes to the organophosphates. This concern is valid in cases when organophosphates are present, and the antidote <u>is</u> required, and also in the cases when the organophosphate is not present but the antidote is administered either inadvertently or prophylactically.

The primary ocular effects of atropine (whether applied topically as in ophthalmology or systemically as in anesthesia and in the present case) are paralysis or paresis of accommodation and dilatation of the pupil. These effects may be prolonged (lasting many hours) and may produce changes in functions such as visual acuity, contrast sensitivity and night vision.

Little is known about the ocular side effects of systemically administered atropine. In anesthesiology, atropine is routinely administered in doses of approximately .4 mg by intramuscular injection, but the anesthesiologist is not greatly interested in the effect of the drug on the eye or on visual performance. Mirakhur (1978) examined the ocular side effects of atropine administered intramuscularly. He found that the amplitude of accommodation was decreased and that pupil size was increased by .5, 1, & 2 mg doses of the drug. The effects were prolonged, and were still evident six hours after injection.

Headley, (1982) has reviewed the effects of systemically administered atropine on visual and physiological performance, as well as subjective and cognitive variables. He lists a number of early studies showing that systemically administered atropine increases pupil size and decreases the amplitude of accommodation in doses of 2 mg and above. The accommodation effect appears to be dose dependent; by comparing the percentage of effect in individuals across studies he notes that at a dose of 2 mg, 39% of subjects report problems with near vision, and at a dose of 4 or 5 mg all subjects had some difficulty with near vision.

These visual problems may be the basis for the performance decrements in map and compass reading tasks reported by Moylan-Jones, (1969). It is however not clear if this performance decrement is related to visual factors or to perceptual disorders and disorientation reported by some of the volunteer subjects, who received 6 mg of atropine in three 2 mg injections.

The dose level necessary for protection against exposure to organophosphates is 2 mg or more. We have conducted two series of experiments, one exploring the changes in visual function which are produced by intramuscular injection of 2 mg of atropine, and the other exploring the effects of these visual function changes on performance tasks which are related to real world activities. Our findings indicate that although atropine at the 2 mg dose does produce changes in ocular function, these changes are not reflected in the performance tasks which we have chosen.

EXPERIMENT I

METHODS

General protocol: Ten male subjects, ranging in age from 20 to 33 years, were used in this set of measurements. Each subject was given atropine on one day and a placebo on a second day, with at least 48 hours between test days. The order of administration of drug and placebo was known only to the attending physician in order to conform to standard double-blind experimental protocol. The atropine dose was 2 mg per 70 kg bodyweight injected intramuscularly. Isotonic saline was used as the placebo. Pulse and blood pressure were measured at intervals during the

test day. Subjective intoxication was evaluated by asking the subjects to rate how "high" they felt on a scale of 0 to 100, where 0 was normal and 100 was as "high" as they had ever been before. The "highness" rating was obtained several times during the test day.

The battery of vision tests described below was administered four times; once before injection, and three times following injection at 30, 120, and 240 minutes. Functions measured were:

1. Accommodative Amplitude - With the left eye patched, the subject brought a target containing fine print towards the corrected right eye until the print "first appeared blurred". The distance between the target and the spectacle plane was measured. The task was repeated three times and an average accommodative amplitude in diopters was computed.

2. Accommodative Dynamics - The subject's right eye was aligned with the optical stimulus and measurement systems of the SRI optometer (Cornsweet & Crane, 1970) using a bite bar independently adjustable for the x, y, and z axes. Fixation targets were 10/40 size Landolt C's having a contrast of 70% and a background luminance of 3.5 cd/m^2. To calibrate the optometer output, the subject was directed to "make clear" a projected Landolt C having a vergence stimulus of one diopter, and then to "make clear" the same target with a vergence stimulus of two diopters. The change in voltage output of the SRI device then indicated one diopter of accommodative effort. If the voltage change fell within the range of typical values, the subject was directed to "make clear" a series of vergence changes in one diopter steps starting at zero diopters, going to four diopters, and then returning to zero diopters in one diopter steps. Vergence steps occurred every 3.5 seconds. The voltage output, (accommodative change), was sampled every 40 milliseconds by a digital computer which controlled the experiment. The digitized data and a scale based on the initial subjective calibration was plotted for each run.

3. Heterophoria and ACA Ratio - The subject binocularly viewed a 10/25 letter on a printed eye chart while wearing his habitual correction. The distance phoria was measured by alternate occlusion and neutralization of eye movement with prisms when necessary. Similarly, the near phoria was measured by alternate occlusion while the subject viewed a pencil tip at 40 cm. The interpupillary distance (P.D.) was measured and the ACA ratio computed using the formula: ACA = (Near phoria-Dist. phoria) /2.5 + P.D.

4. Pupil Dynamics - The subject viewed a 10/100 Landolt C with the right eye. A septum between the eyes shielded the right eye from direct illumination by a high intensity stimulus lamp which was switched under computer control. A low light level video camera produced a magnified image of the right eye. A pupillometer (based on a design by Saladin 1978) was used to obtain a voltage signal proportional to pupil diameter. The experiment consisted of three consecutive pupil measurement periods, the first, a prestimulus period of 2.4 seconds, the second with the stimulus light on for 3.2 seconds, and the last, a recovery period of 6.8 seconds. Digitized samples were taken every 40 msec by the computer controlling the experiment. The data were stored on magnetic tape and plotted for each run.

5. Static Visual Acuity - The subject monocularly viewed a screen at three meters while wearing his habitual correction. A graded series of Landolt ring slides with randomly oriented gaps was projected under computer control and the subject indicated the location of the gaps in the targets using push buttons. The test program utilized a staircase method for threshold measurement, and used six reversals as the endpoint criterion. The program computed the % Snell-Sterling acuity (Snell & Sterling, 1926) and minimum angle of resolution threshold from mean of the six reversal points. Target contrast was 70% and background luminance was 3.5 cd/m^2.

6. Refractive State - With the subject wearing his usual correction, the 10/20 letters of an eye chart at 10 feet were observed as increasing amounts of plus sphere were added before the right eye. The left eye was occluded. The weakest powered lens which made the 10/20 letters subjectively unreadable was taken as the test endpoint.

7. Contrast Sensitivity Function - The subject monocularly viewed a CRT screen subtending six degrees at 57 centimeters. The average screen luminance was 10 cd/m^2. Vertical sine wave gratings having a spatial frequency of 1, 3, 5, 10, and 20 cycles/degree were presented in turn; threshold for grating detection was determined for each stimulus spatial frequency. Each stimulus presentation consisted of a warning tone followed by a time delay of 1500 msec. Then came two 250 msec presentations of the stripes separated by 250 msec and an end-of stimulus tone. The subject pressed one of two buttons indicating whether he had seen the stimulus or not. The contrast of the grating was under computer control, and was

increased or decreased according to the subjects responses. The staircase method was used to track threshold, which was computed from the average of 5 reversals at each spatial frequency.

8. Glare Recovery - The first part of this test involved measuring the detection threshold (using the method of adjustment) for a 5 minute of arc test spot (which was flashed at 4 Hz). Three settings of spot contrast were made by the subject. The subject then looked directly at a glare source having a luminance of 5.5×10^4 cd/m^2, which was turned on for 10 seconds. At the end of the glare exposure, he looked at a uniform field with fixation markers on it; at the center of these fixation markers there was a 5 min of arc spot flashing at 4 Hz. When he had recovered visual sensitivity to the point where he could detect the spot, the subject pressed a button and this time was recorded. Simultaneously the contrast of the spot was decreased by a fixed amount so that it was below threshold and the recovery process continued until the subject could detect the spot once more. At this point he pressed the button again. This time was recorded, and the contrast of the spot was again decreased so that it was below his threshold. This procedure was repeated so that 5 glare recovery times were measured after the single exposure to the bright light source.

9. Intraocular Pressure - The subject's right eye was measured three times using the American Optical "air puff" or noncontact tonometer (Wittenberg, 1973). The three readings were averaged.

10. Depth Perception Test - The subject binocularly viewed random dot polarized patterns of the Randot™ Stereotest while wearing his habitual correction and appropriate polarizing filters. The test was held at the subject's reading distance (40-50 cm) and illuminated by a nearby high intensity desk lamp. Test patterns 1-8 were viewed in order, the subject indicating which spot appeared to "float above the page". At times the test patterns were administered upside down to limit test pattern memorization. This test measures stereoacuities to 20" of arc.

11. Color Matching Test - The subject monocularly viewed two spots of light, one derived from a yellow light emitting diode (LED), and the other from a mixture of light from a red and a green LED. The spots were adjusted in color and brightness in order to make a color and brightness match. The brightness and color settings were obtained for three matches at each test session.

12. Saccadic Eye Movements - The subject had his eye movements monitored using an infra-red limbal sensing device (described by Brown et al, 1977) and made a series of 20 eye movements to targets placed 10° apart. The eye movement waveforms were saccadic sampled by a digital computer at 2 msec intervals. Amplitudes, latencies and saccadic eye movement velocities were calculated.

13. Postural Stability - The subject stood on a 2-axis "deformable" platform (Shipley and Harley, 1971) with his feet side-by-side and attempted to maintain as steady a stance as possible. The outputs of strain gauges attached to the axes of the platform system were amplified and input to a digital computer for analysis. Data were input at a 10 Hz rate for 12 seconds; the standard deviation of the antero-posterior and lateral waveforms were calculated and used as an index of postural stability.

RESULTS

Atropine produced small but measurable effects on accommodation and pupil size when administered to volunteer subjects by intra-muscular injection, at a dose level of 2mg/70kg of body weight. The effects persisted for more than 4 hours. Atropine produced short-lived increases in pulse rate, and induced a mild state of subjective intoxication in the 10 subjects used in this experiment (see methods for a description of the subjective "highness" scale). These effects were present for 2-3 hours. The tests used in these experiments were tests of basic visual function, and did not include significant cognitive, decision or memory components.

The nonparametric Walsh test was used to test the significance of the differences between atropine and placebo data. Possible diurnal effects or day-to-day performance level shifts were subtracted out first, by subtracting pre from post- injection data to obtain post-pre changes in performance for each subject. The corresponding placebo and atropine post-pre changes were used as matched pairs for the Walsh test. Atropine-placebo differences were ranked to determine if they were significantly different from zero for all subjects with valid matched data.

The effect of atropine on the pulse was statistically significant at 30, 90 and 210 minutes following injection (see Fig. 1, error bars indicate one standard deviation from the mean). Thirty minutes after injection the mean pulse difference was 27 beats/min, ($p = .008$). The peak difference of 39 beats/min occurred at 60 minutes postinjection. By 210 minutes the difference had decreased to 11 beats/min, ($p = .031$).

There did not appear to be any systematic effects of atropine on blood pressure as a function of time after injection. However, diastolic blood pressure was raised some 5 to 8 millimeters of mercury above the placebo level throughout the test day period. This effect is probably due to anticipation or anxiety effects in some of our subjects, (see Fig. 2).

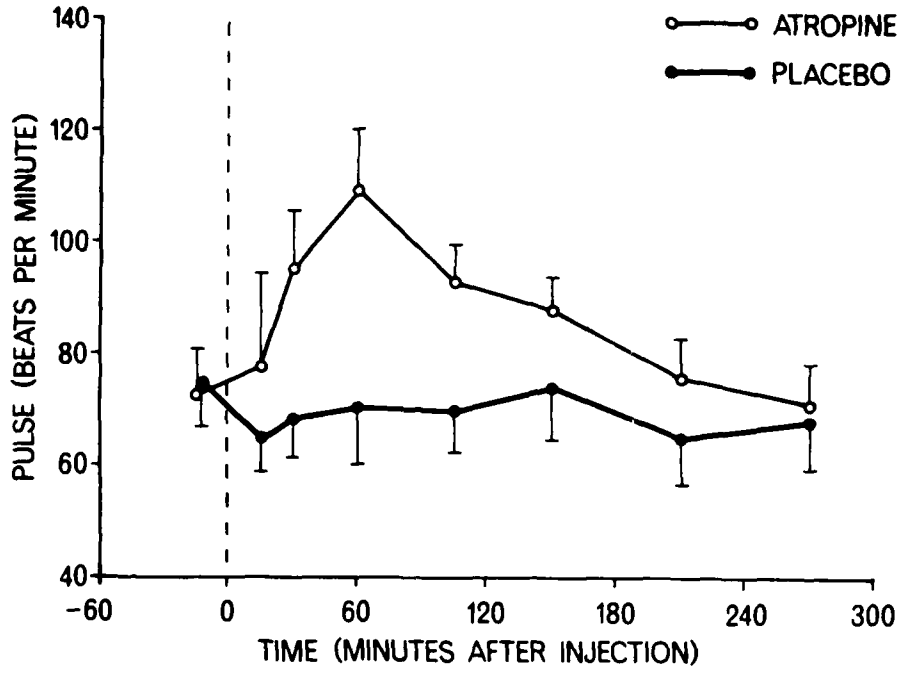

FIGURE 1. Pulse rate averaged across subjects.

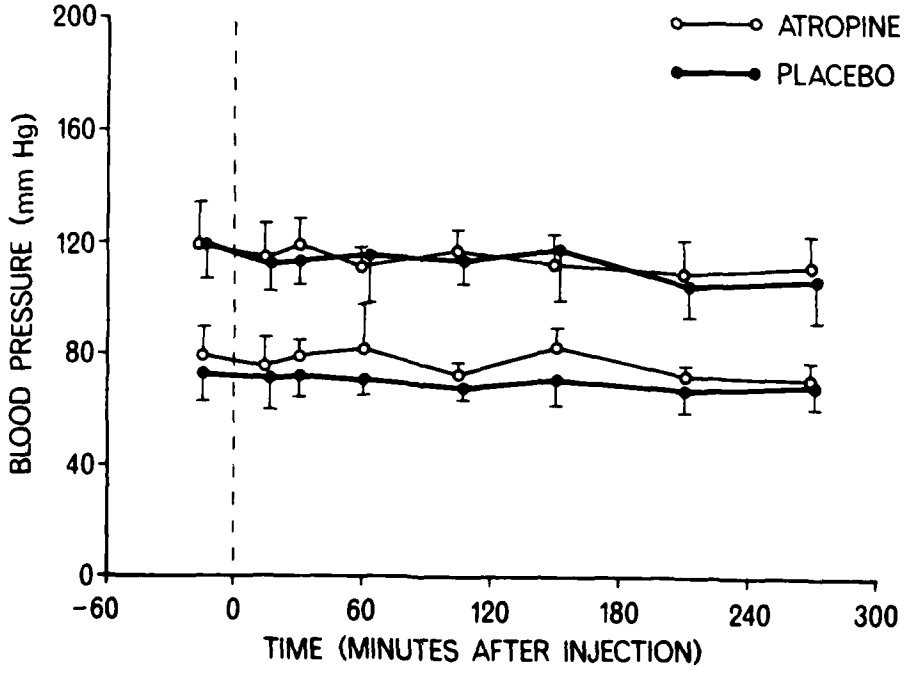

FIGURE 2. Systolic and diastolic blood pressure averaged across subjects.

Our subjects reported weak psychoactive effects with atropine and none reported any effects with the placebo. "Spaced" or "buzzy" feelings were reported half an hour after injection and persisted on the average for 3 hours (see Fig. 3). Onset of the psychoactive effects was quite gradual. The mean high rating was 11 although two subjects reported ratings of 0 or no "high" effects at all. The highest rating that any subject reported was 30 (maximum high rating= 100). All subjects were able to function in the laboratory tests, and informal reports indicated minimal interference with other aspects of motor and mental performance.

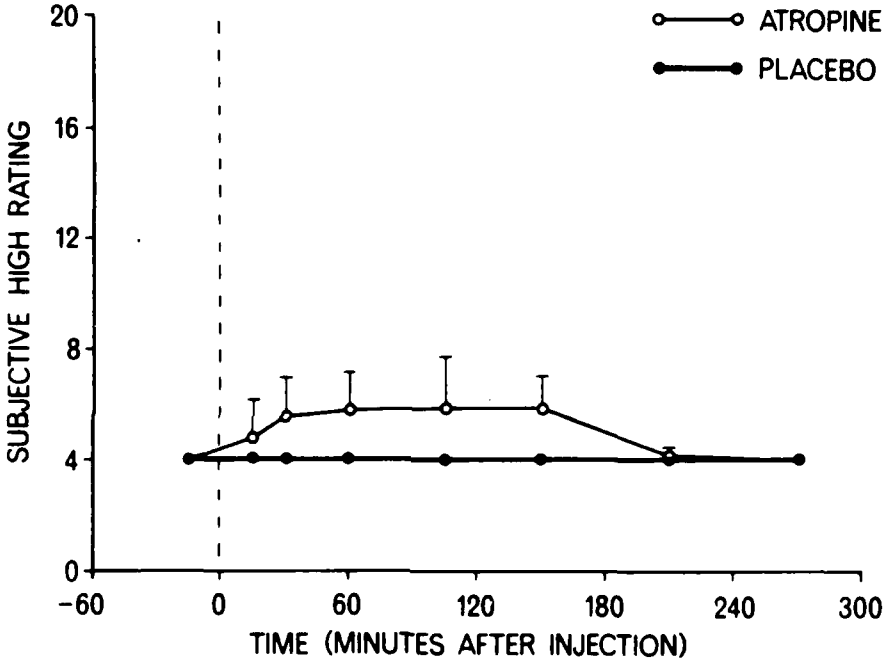

FIGURE 3. Self-rating of "highness" averaged across subjects.

A significant change in the near point of accommodation occurred by thirty minutes after injection of atropine (see Fig. 4). The average accommodative loss was 1.2 diopters, ($p = .004$). At 120 minutes the loss had increased to 1.5 diopters, ($p = .051$) and at 210 minutes the loss was 1.6 diopters, ($p = .004$). The averaged data indicate that there is a small but definite loss in accommodative ability that shows no apparent recovery four hours after injection; only two out of nine subjects showed some recovery of accommodation at four hours.

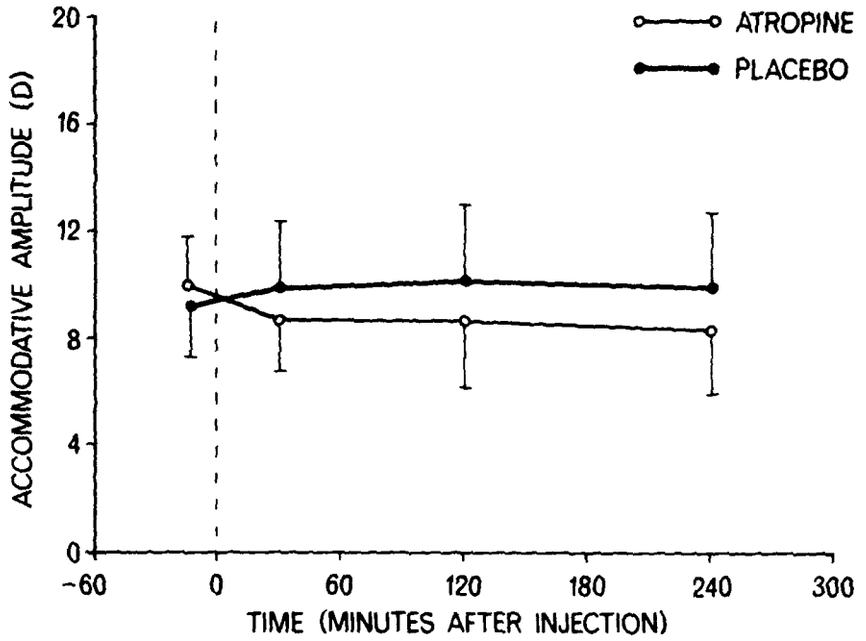

FIGURE 4. Accommodative amplitude averaged across subjects.

Figure 5 shows that atropinized subjects had a small but significant reduction in their measured accommodation for 4D of accommodative demand. Subjects had an average decrease in exerted accommodation (compared to placebo) of 0.35D at 30 minutes post- injection ($p = .031$ $N = 6$), and 0.29D at 240 minutes after drug administration ($p = .031$; $N = 6$). These measurements of dynamic accommodation confirm and extend the more clinically based measures of accommodative near point (see Figure 4 above). They show that there is an atropine-induced lag of accommodation across a range of accommodative stimuli from 2 to 4 diopters for at least 4 hours after drug administration. There were no significant differences in latencies or velocities for one diopter steps in accommodation between atropine and placebo sessions.

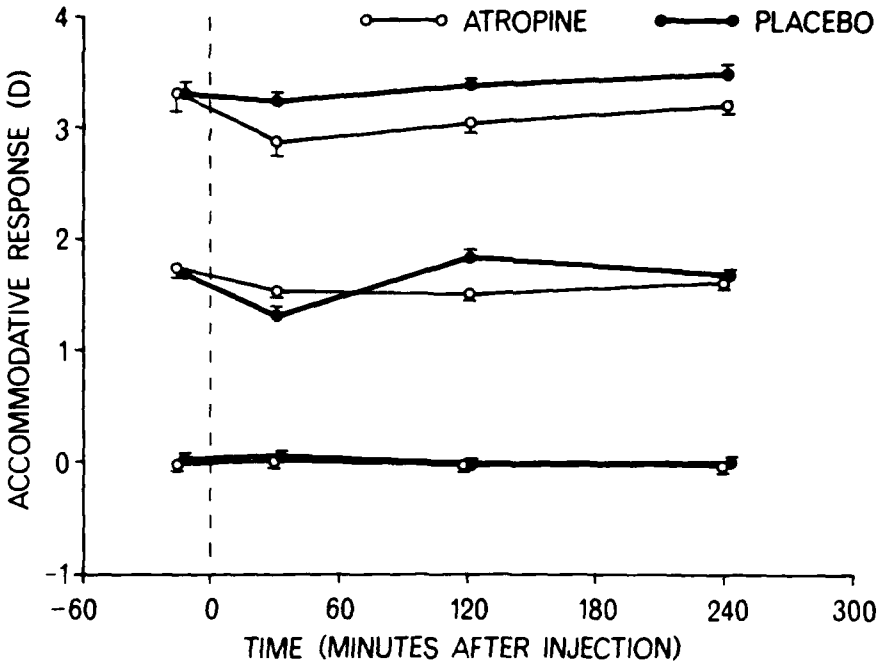

FIGURE 5. Dynamic accommodation task. Averaged response to stimuli of 0, 2, & 4 diopters averaged across subjects.

Atropine produced no significant change in ocular balance (heterophoria) either at distance or at near in our subjects. Fig. 6 shows these data. Of course, since there is no change in heterophoria with the drug, there is also no change in ACA ratio.

Atropine produced a significant dilation of the pupil within 30 minutes and averaged data indicate no recovery within four hours of injection (see Fig. 7). The average increase in pupil diameter 30 minutes after injection was 1.0mm, ($p=.004$, $n=8$; 43% increase in area). The increase was 1.3mm at 2 hours, ($p=.004$, $n=9$; 54% increase in area) and 1.4mm at four hours, ($p=.004$, $n=9$; 58% increase in area). One subject showed no dilation effect with atropine.

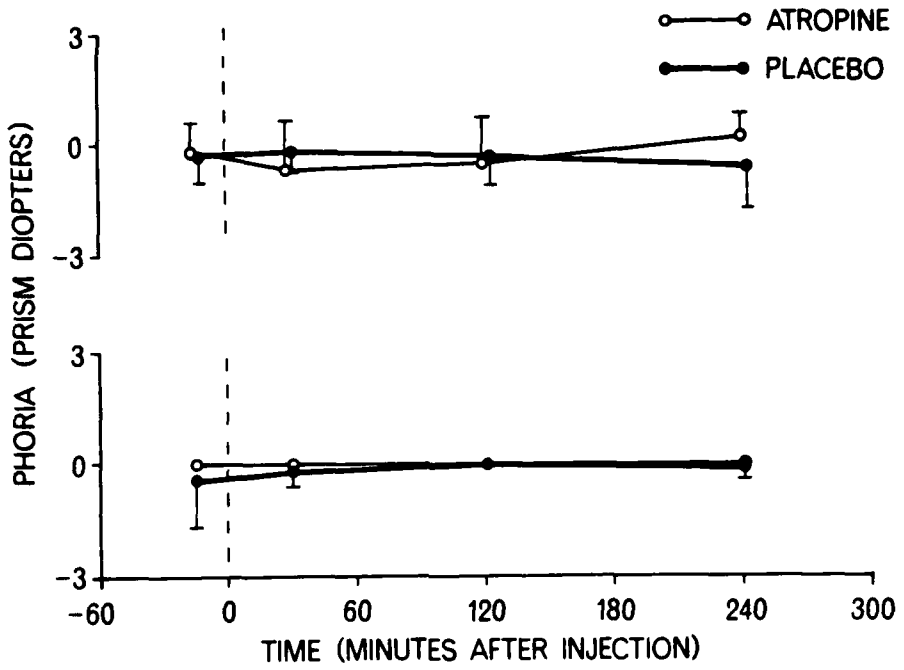

FIGURE 6. Phoria at 0.4 meters (top) and at 3 meters (bottom) averaged across subjects.

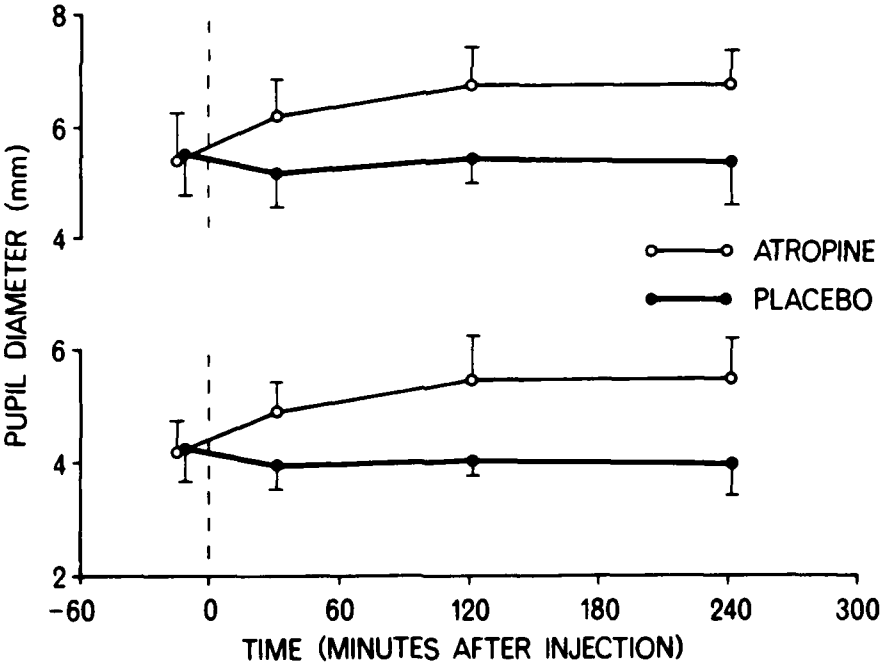

FIGURE 7. Pupil diameter during pre-stimulus (top) and stimulus (bottom) conditions averaged across subjects.

The effect of atropine on pupil diameter was essentially constant across the different phases of the dynamic pupil response task. Atropine produced large and significant changes in pupil diameter before the onset of the light stimulus, during the stimulus and after the stimulus, at all post-drug measurements times. The subjects showed a small reduction in the ability to constrict the pupil for contralateral light stimulation. These data are shown in Fig. 8, and it is evident that the change in the ability to constrict the pupil to light stimulation follows approximately the same time course as the change in pupil diameter itself. Latencies of constriction or dilatation were not significantly altered by atropine, nor were the velocities of these changes in pupil size affected.

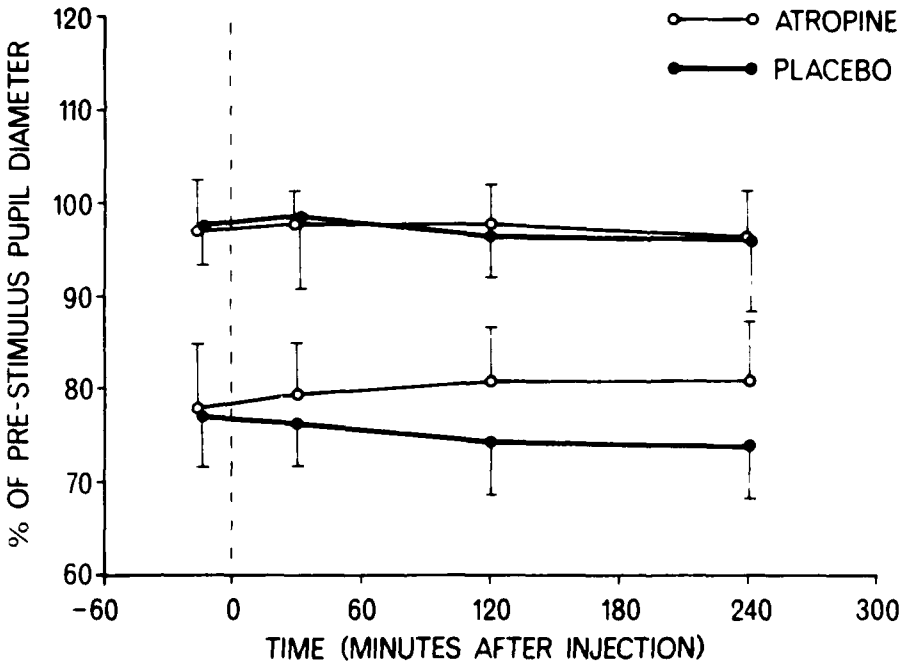

FIGURE 8. Percent change in pupil diameter during redilation (top) and contraction (bottom) averaged across subjects.

Static visual acuity was unaffected by atropine. These date are shown in Fig. 9, and substantiated by the data of Fig. 10, which shows the amount of plus sphere used to produce subjective blur of a 10/20 line. There is no change of practical or statistical significance in either set of data.

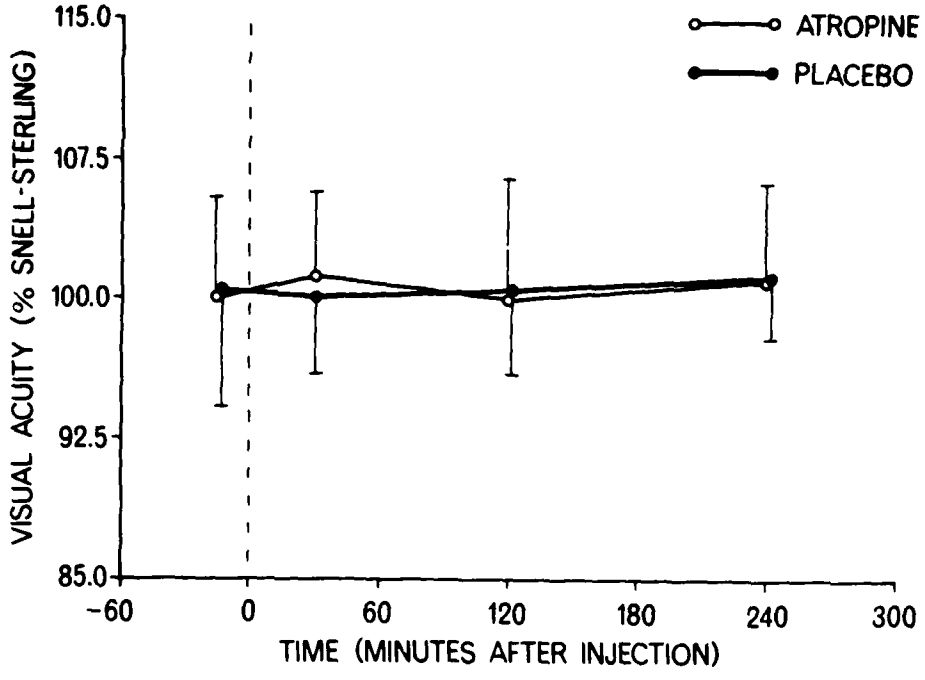

FIGURE 9. Static visual acuity averaged across subjects.

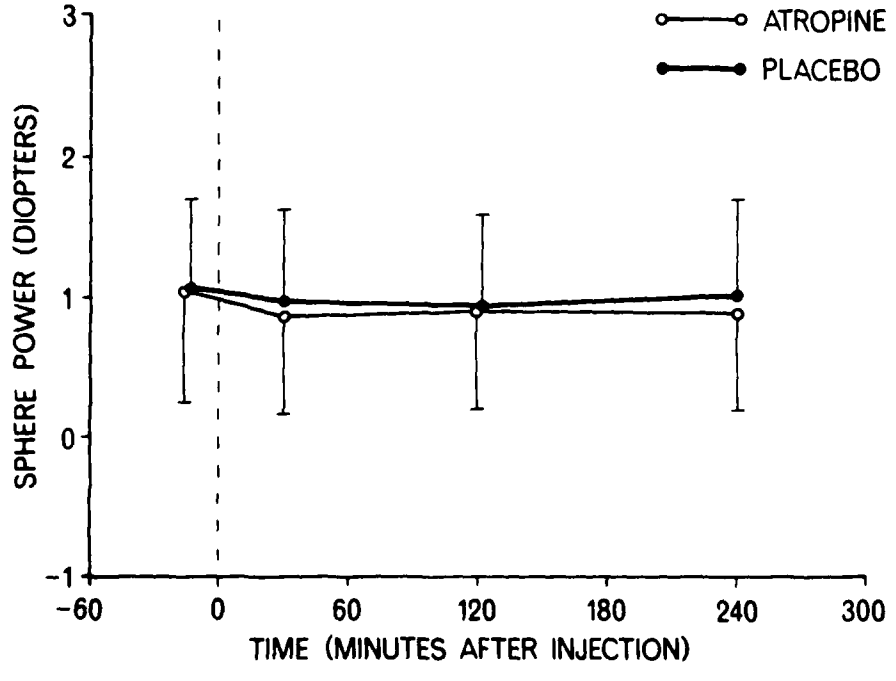

FIGURE 10. Sphere power to blur acuity to 10/15 averaged across subjects.

There were no significant differences in the contrast sensitivity function (CSF) for atropine subjects at 30 and 120 minutes after injection. At 240 minutes, however, the data appear to indicate a small but consistent loss in sensitivity across all frequencies. When the Walsh test was applied, only the data for the frequencies of 5 c/d (cycles/degree) and 20 c/d showed significant differences, (5 c/d $p = .055$; 20 c/d $p = .023$). Figure 11 shows these data.

As a control for changes in refractive state, which influence the measured glare recovery times, we also measured contrast thresholds for a 5 min of arc flashing spot prior to the glare recovery measure. These measures of contrast threshold showed no change as a function of administration of atropine. Time constants of the glare recovery process were computed from the measured recovery times. The only significant difference between drug and placebo data occurred 30 minutes after injection, ($p = .031$), however all of the atropine test data show prolonged time constants (see Fig. 12).

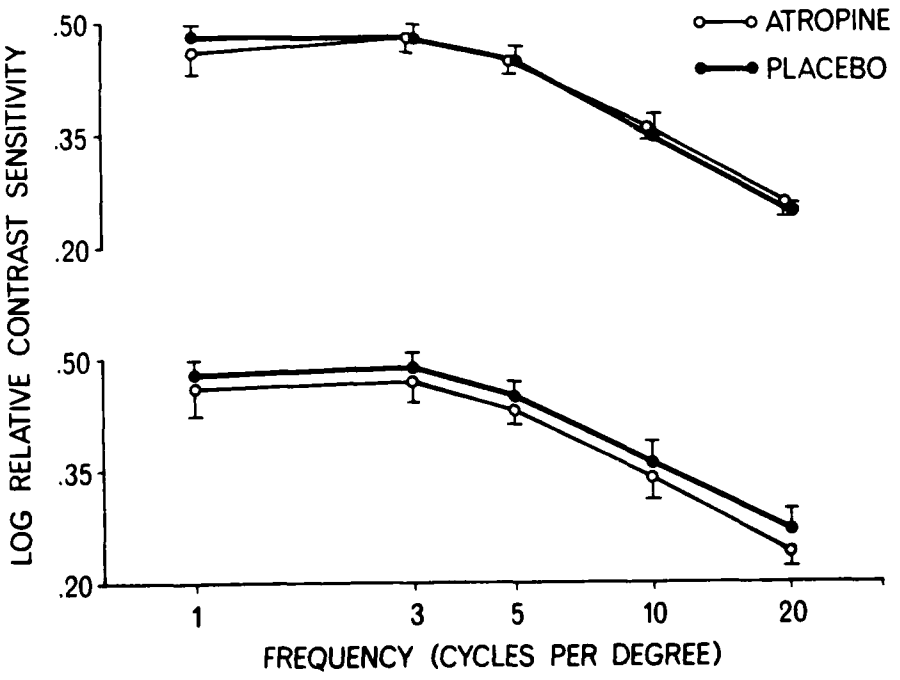

FIGURE 11. Contrast sensitivity function for the pre-drug session (top)& 240minutesafter injection(bottom)averagedacross subjects.

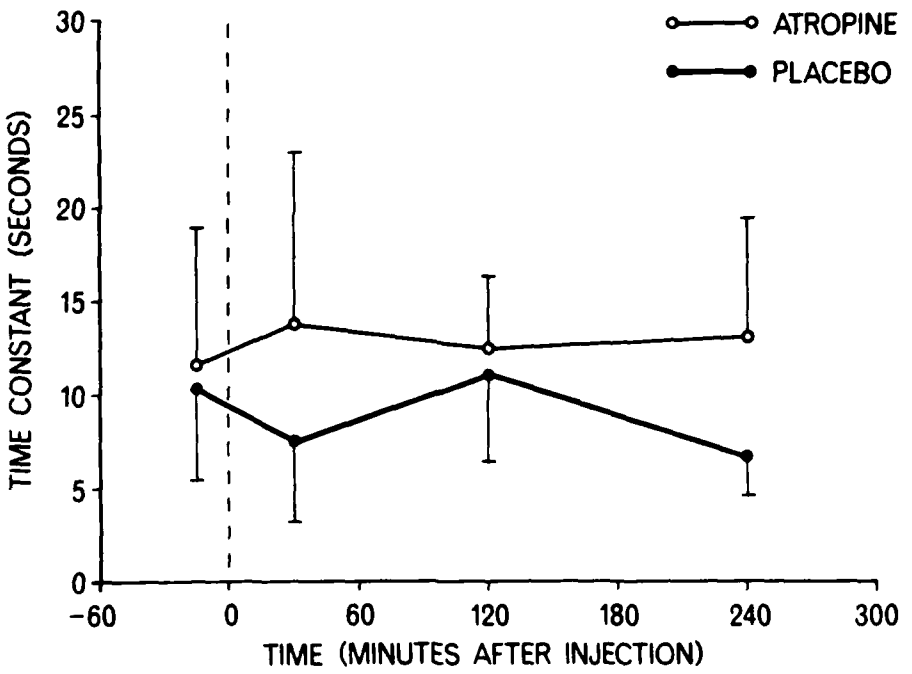

FIGURE 12. Glare recovery time constant averaged across subjects.

Atropine produced slight but statistically insignificant decrease in intra-ocular pressure as a function of time after drug administration. Intra-ocular pressure appeared to be diminished by approximately .5 to 1 mm Hg, and the differences between the atropine treatment and placebo data were sustained for 4 hours, (see Fig. 13).

There were no differences between atropine and placebo data on the Randot test of stereoscopic acuity. However, this test is relatively coarse in its measurement scale, and changes of stereo acuity of less than 20" of arc may have occurred and been undetected.

We were unable to demonstrate any changes in color perception using our anomaloscope, which is based on the Rayleigh equation. There were no drug induced effects either on color match or perceived brightness of the stimuli.

Saccadic eye movements made in response to targets moved at random times after a warning tone were unaffected by atropine in accuracy, latency or velocity after 2mg of atropine. The data shown in Figure 14 show a tendency toward greater variability in the atropine data, but no significance is attached to this finding.

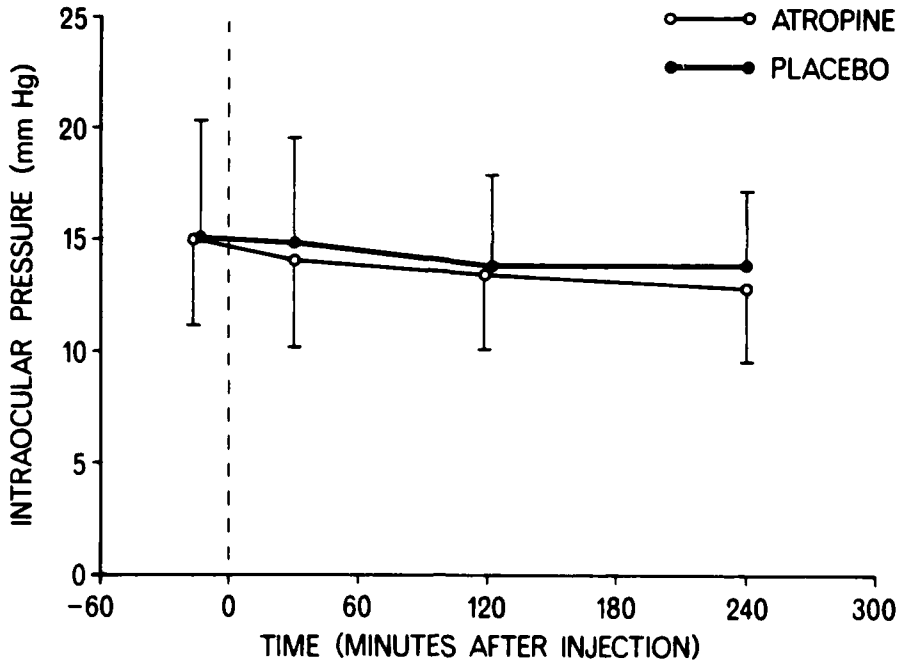

FIGURE 13. Intraocular pressure (AO NCT) averaged across subjects.

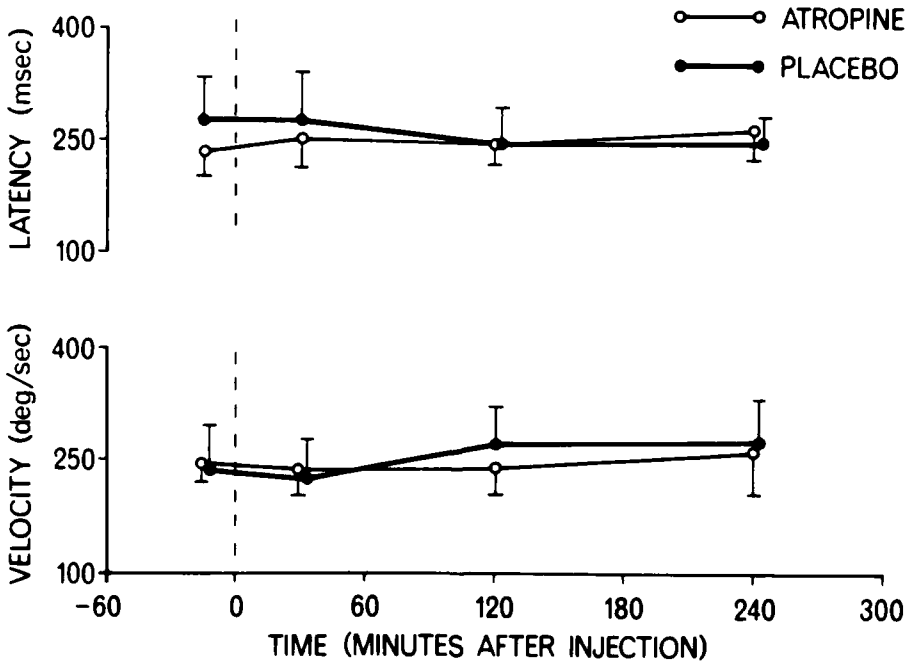

FIGURE 14. Saccadic latency (top) for ten degree stimulus movements and average velocity (bottom) averaged across subjects.

Atropine also has no significant effects on postural stability as measured with our 2-axis postural stability assessment system. These data are shown in Figure 15; the subjects show greater stability with eyes open than eyes closed, but no differences between placebo and drug treatment data.

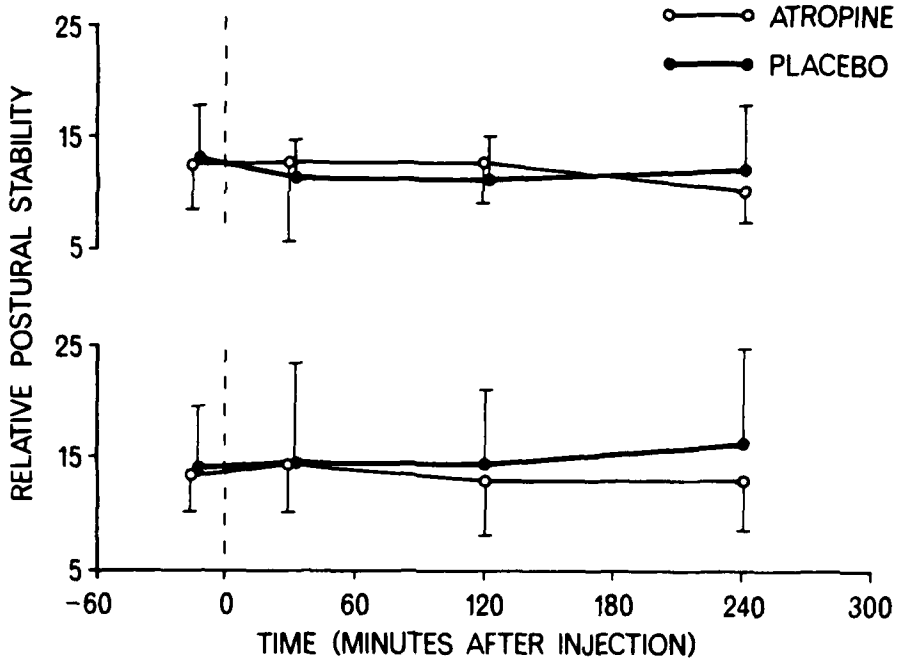

FIGURE 15. Lateral postural stability with eyes open (top) and closed (bottom) averaged across subjects.

We have demonstrated long lasting changes in accommodative function, pupil size, and the contrast sensitivity function which though relatively small, may have effects on tasks such as those performed by military personnel. We therefore conducted a second experiment which involved two separate tasks, embodying many aspects of real world performance. These task components included rapid changes of accommodation, identification of targets, measurement of choice response times and a motor task where precise responses were necessary. One of the tasks was carried out with the subject and the task in motion, so that reflex eye movements produced by the vestibular system had to be suppressed. We found that atropine produced approximately the same subjective and general physiological changes noted in the first experiment, but there were no significant effects on performance of these more complex tasks.

EXPERIMENT TWO

METHODS

General protocol: Six male subjects ranging in age from 21 to 32 years were used in these experiments. Each subject was given atropine on one day and a placebo on another day with at least 48 hours between test days. The order of administration was known only to the attending physician in order to conform to our standard double-blind experimental protocol. The atropine dose was 2 mg per 70 kg of bodyweight, given intramuscularly in the upper arm. Isotonic saline was used as the placebo.

The testing schedule for each day consisted of three sessions, each session consisting of two visual performance tasks, a questionnaire, and measurements of pulse and blood pressure. The first session was completed just prior to the injection. The second and third sessions began at one and four hours following the injection. Each session took approximately 30 minutes and the intervening time was spent by the subjects in sedentary activities such as reading.

Accommodative response task: This visual performance task required each subject to repeatedly change his state of accommodation from far to near and back again in order to identify the orientation of single randomly selected Landolt rings. The response time for the identification of each target was measured and averaged over a set of twenty stimulus presentations. Incorrect responses were tabulated but not included in the averaged response times. A second set of twenty presentations was made with a reduced target contrast. The two contrast levels were 73% and 40% with a background luminance level of 3.5 cd/m^2. Landolt rings, 10 minutes of arc in total extent (20/40 Snellen), were presented, at either zero or 2.5 diopters of optically produced divergence, thus optically placing the target at infinity or 40 cm from the eye.

In the assessment of accommodative responses in this experiment and in assessment of visual search times in the next experiment, the median was used for each set of data, since it better represents the central tendency of these skewed distributions.

Visual search task: The visual search task consisted of viewing 100 randomly positioned dots on an oscilloscope screen and locating a single dot which was twice as bright as the other background dots. The time taken to find this dot was measured. The brighter dot occupied one of 772,500 possible positions in a 1024 by 1024 display space subtending 5 degrees of arc on each side. (Targets were not presented near the edges of the display, since it has been shown that such targets are less likely to be detected, and thus greater variance would be introduced into the data, Leibowitz, 1973). This search task was repeated until the subject had correctly located the brighter dot 50 times.

To perform the task the subject pressed a button, which caused a random dot pattern display to be presented. He then searched the display until he had located the target, then released the button. The time during which the button was held down was measured (with a resolution of 20 msec). Whether the subject had correctly detected the target was determined by asking him to use a joystick to move a pair of cross-hair lines to the target position on the display. This task was made more difficult by removing all of the dots for two seconds prior to placing the cross-hairs on the oscilloscope screen. This approach forced subjects to rely on short term memory in order to position the crosshairs within a "hit zone" and to have it counted as a correct target identification. A square subtending 54 minutes of arc on a side centered on the brighter dot constituted the "hit zone". The hit zone was outlined on the oscilloscope screen after each response in order to give the subject feedback on the accuracy of his response. Incorrect dot identifications were tabulated as errors but not included in computing

the mean and median response times. Search times, accuracy of positioning the cross-hairs both horizontally and vertically, and number of target identification errors were recorded for later analysis.

To "stress" the subject while performing the search task, he was continuously oscillated in a chair designed to stimulate the vestibular system. The display oscilloscope was mounted on the oscillating chair and thus the subject was required to compensate for, or suppress eye movements induced by the vestibulo-ocular reflex. The chair was rotated back and forth with a sine wave velocity profile which had a period of 1 second and an angular rotation path of approximately five degrees. The room was dimly illuminated to allow peripheral retinal awareness of chair movement. Auditory white noise was used to mask extraneous background noises during testing. The oscilloscope was mounted with the screen 70 centimeters from the subject producing a 1.4 diopter stimulus to accommodation. Dot subtense was approximately 1-2 minutes of arc. The brighter dot had a luminance of 5 cd/m2 and the other dots were half as bright.

Questionnaire and vital signs: After completion of the two visual performance tasks each subject was asked to fill out a questionaire of 17 items, in order to follow subjective awareness of changes in vision, coordination, physiological side effects, and state of mind. The subjects rated themselves in comparison to how they felt at the beginning of each test day. The questionnaire is shown in Figure 16. Pulse and blood pressure were also measured after each session by the attending physician.

SUBJECT INITIALS:____ DATE: / /81

ATROPINE SUBJECTIVE CHECKLIST

Please check the appropriate point on the scale for each of the following areas:

MOUTH	MOIST	1	2	3	4	5	DRY
SKIN	MOIST	1	2	3	4	5	DRY
DISTANCE VISION	CLEAR	1	2	3	4	5	BLURRED
NEAR VISION	CLEAR	1	2	3	4	5	BLURRED
"HIGH"	NOT HIGH	1	2	3	4	5	AS HIGH AS I HAVE BEEN
TEMPERATURE	(COLD)	1	2	NORMAL	4	5	(HOT)
BALANCE	(WORSE)	1	2	NORMAL	4	5	(BETTER)
COORDINATION	(WORSE)	1	2	NORMAL	4	5	(BETTER)
TENSION	(WORSE)	1	2	NORMAL	4	5	(BETTER)
RESTLESSNESS	(MORE)	1	2	NORMAL	4	5	(LESS)
DEPRESSION	(MORE)	1	2	NORMAL	4	5	(LESS)
ANXIETY	(WORSE)	1	2	NORMAL	4	5	(BETTER)
FATIGUE	(WORSE)	1	2	NORMAL	4	5	(BETTER)
CONCENTRATION	(WORSE)	1	2	NORMAL	4	5	(BETTER)
CONFUSION	(WORSE)	1	2	NORMAL	4	5	(BETTER)
FORGETFULNESS	(WORSE)	1	2	NORMAL	4	5	(BETTER)

PULSE ____ BLOOD PRESSURE ____/____

PHYSICIAN'S INITIAL ____ TIME ____:____

FIGURE 16. Subject questionnaire and vital signs record.

RESULTS

As in the previous experiment, atropine produced a significant elevation in pulse rate in the experimental data as compared to the placebo data (p=.016). The effect decreased as a function of time to approximately the same level as pre-drug by four hours after injection. These data are shown in Figure 17. Atropine also produced a mild sensation of "highness" which appeared to persist beyond the time when it had diminished to pre-drug levels in our prior experiment (see Fig.18). This may be an artifact produced by the relative coarseness of the scale used in the present experiment. Dryness of the mouth is another physiological change expected after administration of anticholinergic drugs. Figure 18 also shows the results of self-rated mouth dryness as a function of time after drug administration. Ninety minutes after drug injection there is an elevation in self-rating values which diminishes as a function of time. Motor coordination and fatigue also measured from the self-rating scale show some changes after administration of atropine compared to the placebo values, but these changes are relatively small and not statistically significant, (see Fig. 19).

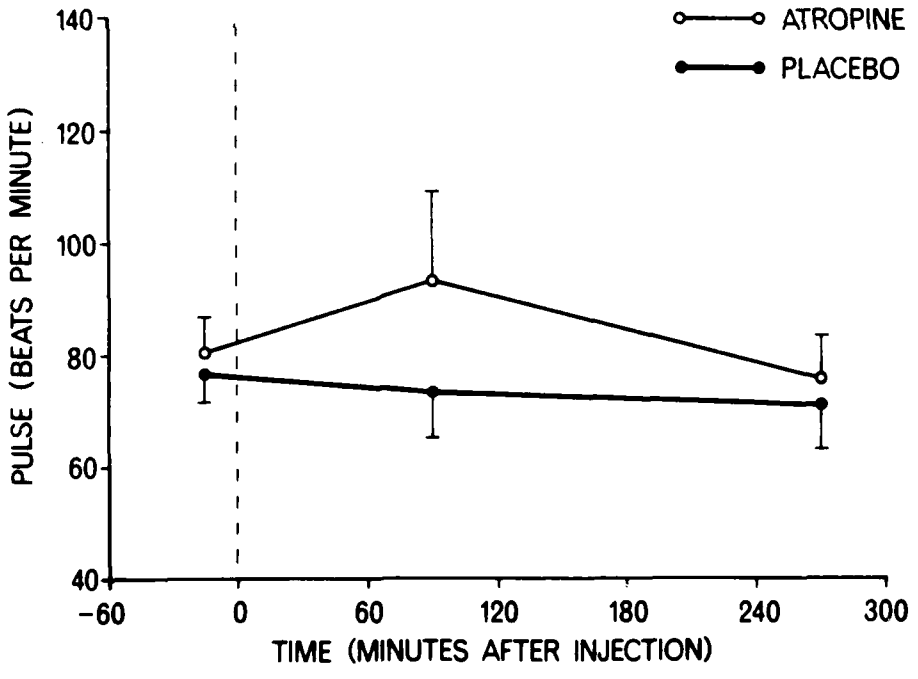

FIGURE 17. Pulse rate averaged across subjects.

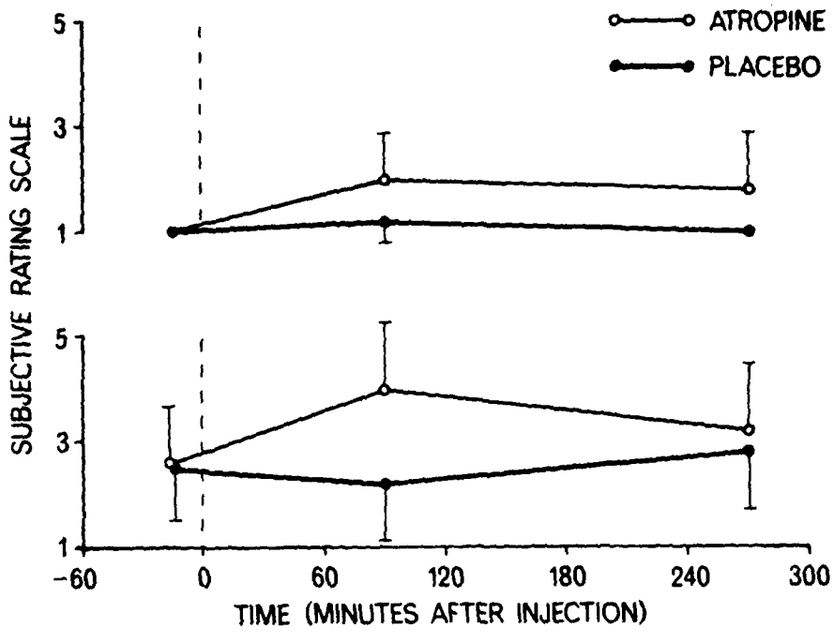

FIGURE 18. Self-rating of "highness" (top) and dryness of the mouth (bottom) averaged across subjects. 1= normal & 5= very high/ very dry.

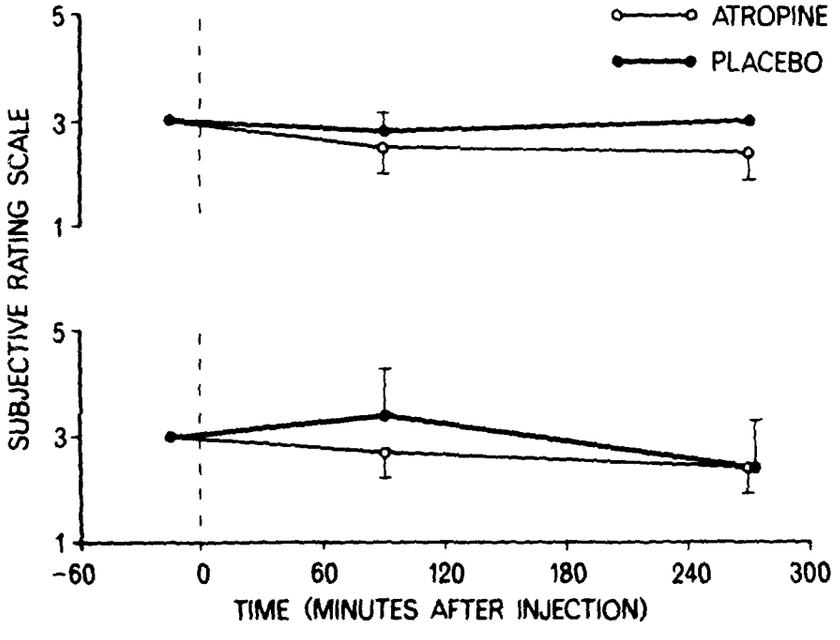

FIGURE 19. Self-rating of coordination (top) and fatigue (bottom) averaged across subjects. 1= worse, 3= normal, & 5= better.

There were no significant changes produced by the drug in the task involving repeated accommodative response and target identification. Representative data are shown in Figure 20. This was true for both positive accommodation (i.e., changing accommodation from 0 diopters to 2.5 diopters) and for negative accommodation. Contrast of the target has a significant effect on response times. Response times are prolonged with the lower contrast targets; the magnitude of this effect is approximately one second (see Fig. 21). It is not clear whether the effect is produced by a longer response time in the accommodation system, in the recognition of target orientation, or in the motor response of the button press.

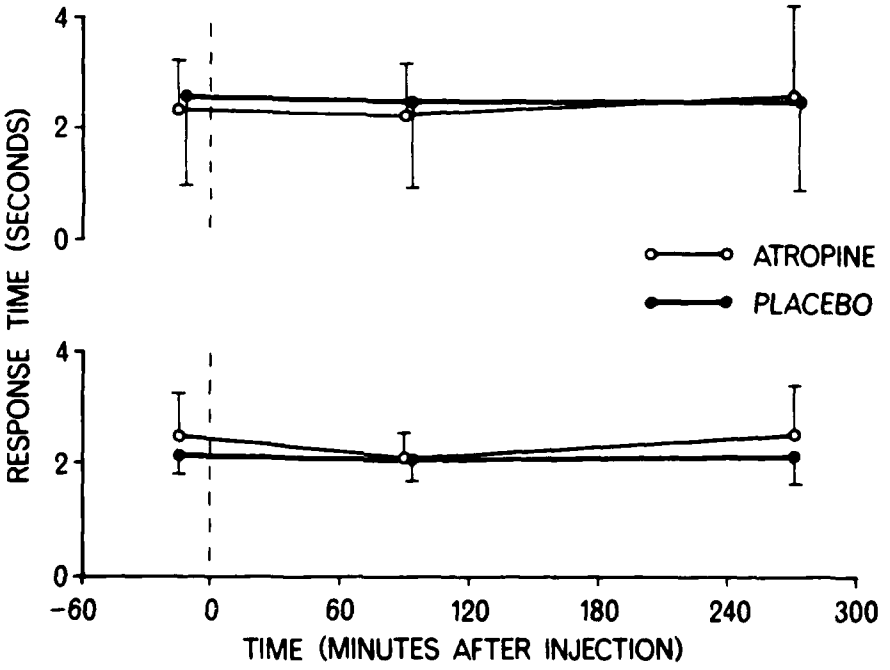

FIGURE 20. Median of twenty response times for positive accommodation (top) and negative accommodation (bottom) averaged across subjects.

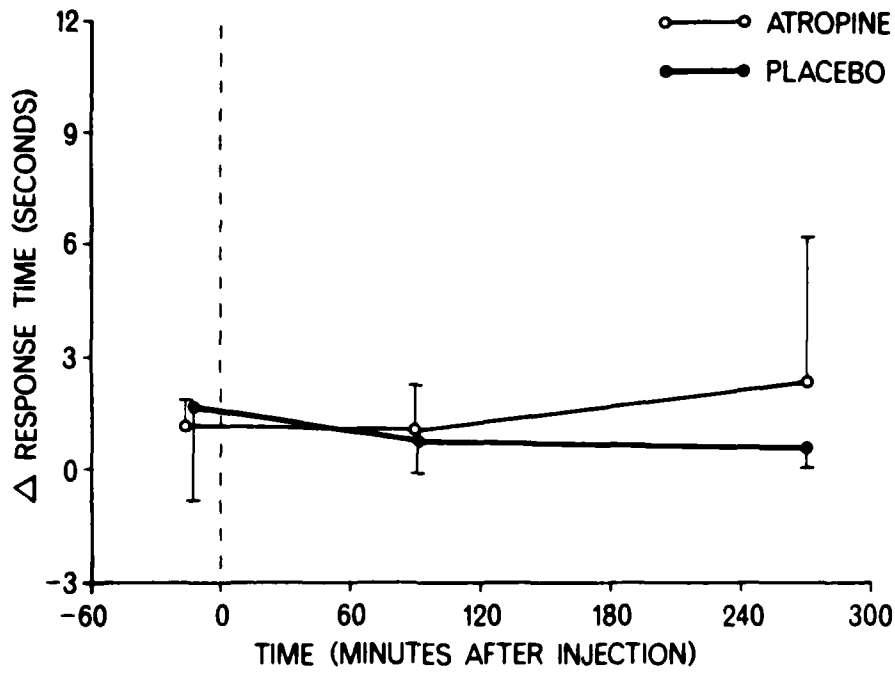

FIGURE 21. Difference in response times for high & low contrast targets for the positive accommodation task averaged across subjects.

In the visual search task atropine did not produce any change in search times, number of target identification errors, or motor response accuracy. Figure 22 shows the median search times for atropine and placebo sessions. There is no significant difference between the atropine and placebo treatment data at any measurement time. Errors in the search task occurred when the subject did not position the cross-hairs within the "hit zone", (X or Y-axis position error of at least 27 minutes of arc). There appears to be an atropine effect on the number of errors in the search task as a function of time after injection, but the difference between the atropine treatment and placebo treatment after drug injection does not reach statistical significance (see Figure 23). The difference between the treatments has diminished almost to zero at the end of the experimental period. The X-axis (horizontal) and Y-axis (vertical) accuracy in cross-hair positioning averaged 25-27 display space units corresponding to 9-10 minutes of arc in both axes (see Figure 24). The atropine data show more variability after injection; this is the only change worthy of note in these data and it is not statistically significant.

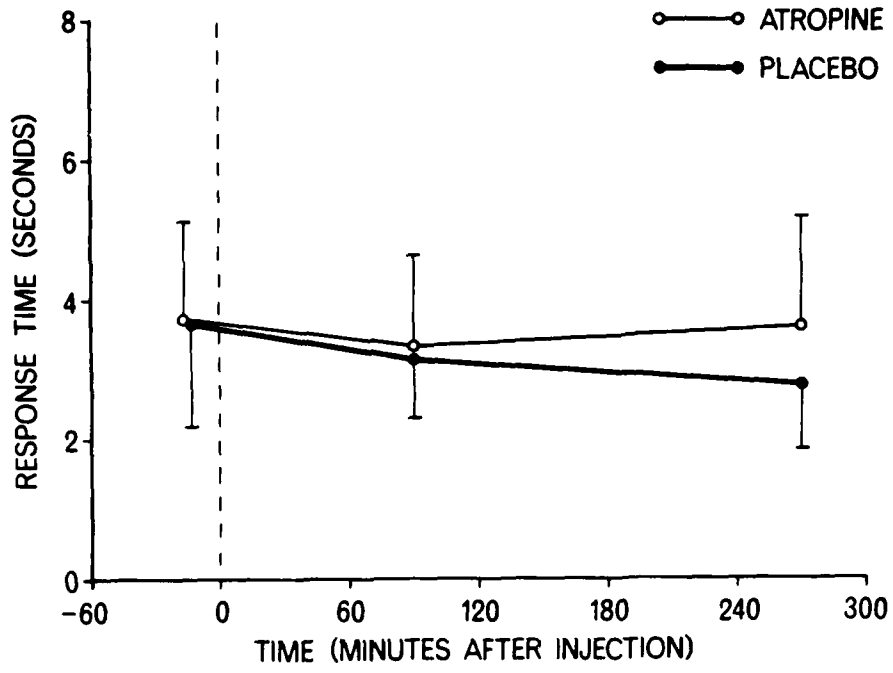

FIGURE 22. Median visual search response time averaged across subjects.

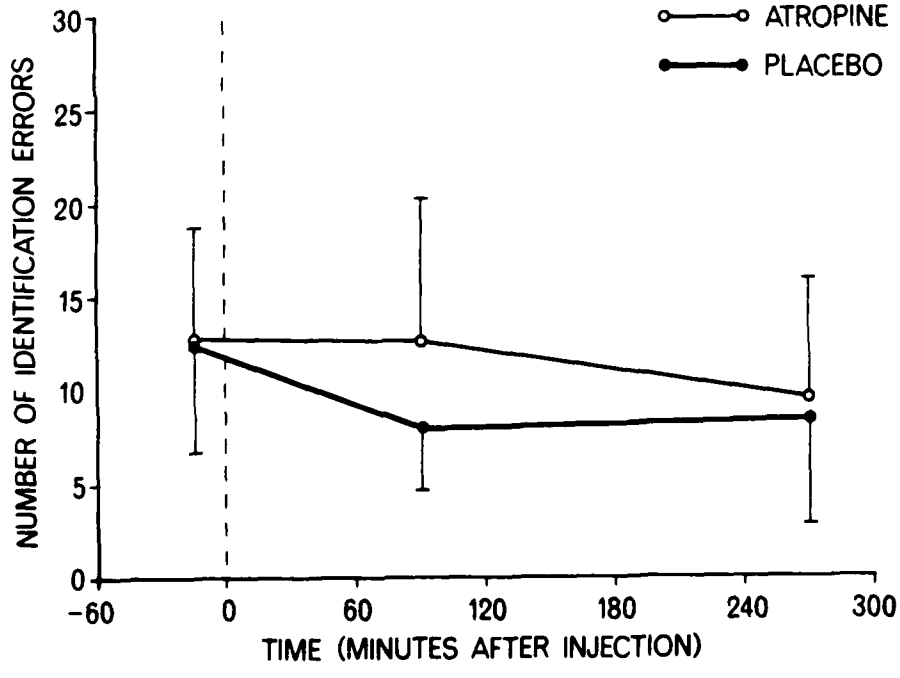

FIGURE 23. Number of identification errors during visual search task averaged across subjects.

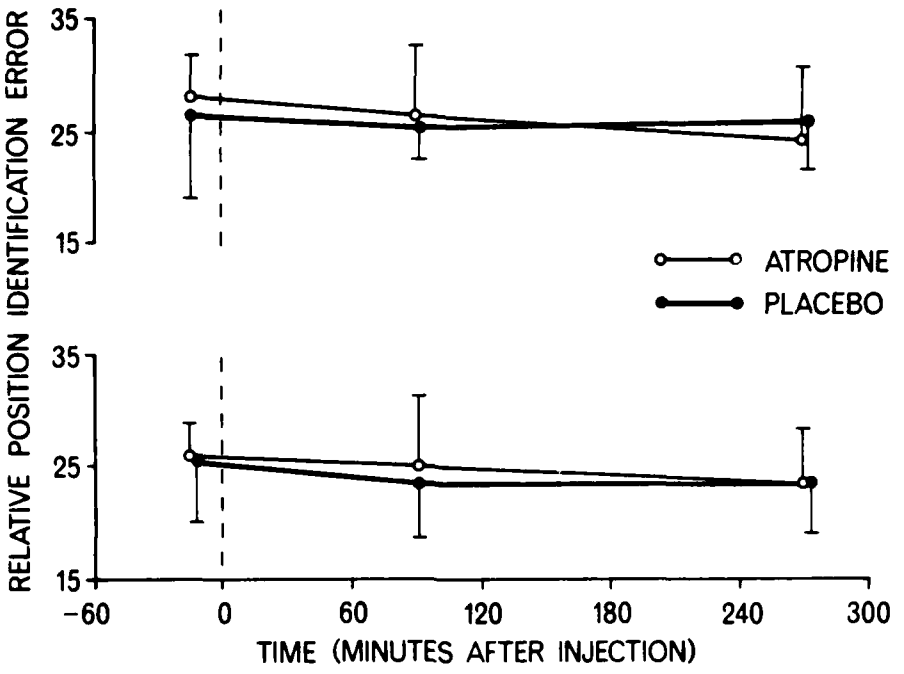

FIGURE 24. Visual search identification accuracy in the X-axis (top) and Y-axis (bottom) averaged across subjects.

The questionnaire items probing depression and tension showed almost no change as a function of either atropine or placebo treatment. Subjects felt that they were less able to concentrate and slightly more confused after administration of atropine, but neither of these changes reached statistical significance, (see Fig. 25).

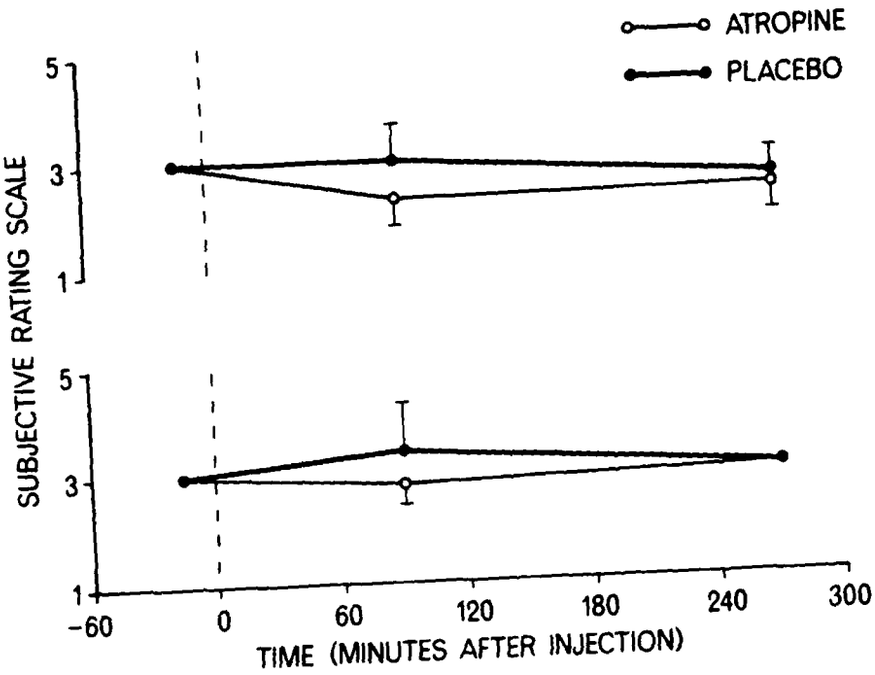

FIGURE 25 Self-rating of concentration (top) and confusion (bottom) averaged across subjects. 1= worse, 3= normal, & 5= better.

DISCUSSION

Our earlier experiments have indicated that systemically administered atropine does produce measurable alterations in visual function. Specifically it reduces the amplitude of accommodation and increases the size of the pupil, for periods in excess of four hours. The current experiments address the question of whether these changes in visual function have any bearing on performance of tasks which have real world analogs. Our data indicate that there is no effect of these altered visual functions on the performance tasks which we have chosen.

Since both of the tasks which we used in the second experiment are relatively complex, we are reasonably confident in predicting that atropine at this dose will have few adverse effects in many military task situations. The first task which we used, an accommodation and recognition task involves the subject detecting a change in target distance, adjusting the accommodation system to refocus the image on the retina, detecting the orientation of the target, making the choice of which button is appropriate to the target orientation, and making a rapid motor response. The visual search task involves ocular scanning of the display, discrimination of the brighter target dot, releasing the display control button, waiting two seconds for cross-hairs to appear, and using a joystick to position the cross-hairs at the target position. These search experiment tasks are carried out in a moving environment, in which reflex eye movements driven by the vestibular system must be suppressed.

Although atropine produced no effects on our performance tasks, which have a substantial accommodation component, there may be personnel who could be affected under certain conditions. Atropine reduced the amplitude of accommodation in our subjects. Pre-presbyopic personnel, in the age range from 35 to 45, who have uncorrected hyperopia and/or a reduced amplitude of accommodation but do not yet have reading glasses may find near tasks such as map reading almost impossible to perform after atropine administration. This deficit would be especially accentuated under poor lighting conditions, and by enlarged pupils.

In contrast to other anticholinergic agents such as benactyzine or marijuana, systemically administered atropine (at 2 mg/70 kg body weight dosages) has few psycho-active effects. Our subjects reported only slight effects of the drug on mental function and indicated that the degree of intoxication would not interfere with any but the most demanding tasks. At higher doses than those used here, effects on visual function and motor coordination could be expected. (See Headley, 1982, for a review.)

Marijuana and benactyzine have pronounced effects on short-term memory but atropine has not. The visual search task used in Experiment 2 contained an element of short-term memory, since the subject had to remember the target position for some two seconds before he could make the appropriate motor response to position the cross-hairs on the display. This was carried out with equal accuracy after atropine or placebo treatments.

Many military performance tasks are of the same order of complexity as those outlined above, although there are military situations in which more complex sequences of stimulus and response must be performed. Will atropine have effects on these more complex tasks? On the basis of our experience with approximately 20 subjects in formal experimental procedures, and informal interaction and questioning of those subjects, we feel that intramuscular atropine at this dose will not produce adverse effects in most military performance tasks. There may, however, be environmental conditions (i.e., conditions producing heat and psychological stress) in which the physiological effects of atropine may be accentuated, and have a negative impact on performance.

LIST OF FIGURES

Experiment 1: 2 mg atropine/70 kg and placebo; N=10 Page No.

Experiment 2: atropine 2 mg/70 kg and placebo; N=6 Page No.

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APPENDIX

This Appendix includes the data that is used in the figures in the main body of this report. Values given represent the mean and standard deviation for a group of N subjects. Times are in minutes pre and post injection of the drug. Other units are noted in each table.

LIST OF TABLES

Experiment 1: Atropine 2 mg/70 kg and placebo; N=10 Page No.

Experiment 2: Atropine 2 mg/70 kg and placebo. N=6

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	72.4	8.9	10	75.0	8.2	10
+15	77.7	16.7	6	64.5	5.7	4
+30	95.3	10.4	9	68.3	7.0	8
+60	109.2	11.1	5	70.3	10.2	6
+105	93.0	6.7	6	69.7	7.3	6
+150	88.0	6.2	5	74.0	9.5	4
+210	75.8	7.3	6	64.7	8.3	6
+270	71.0	7.4	7	67.7	8.2	6

TABLE 1. Pulse rate averaged across subjects. (Data for Figure 1.)

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	119.2	15.1	10	119.6	12.1	10
+15	114.3	12.5	6	112.0	9.9	4
+30	119.1	9.7	9	113.3	7.7	8
+60	111.2	6.6	5	115.3	17.3	6
+105	117.2	7.5	6	113.7	8.5	6
+150	112.6	11.1	5	118.0	18.0	4
+210	109.3	12.4	6	105.3	11.3	6
+270	111.7	11.0	7	107.3	15.6	6
PRE	79.3	10.2	10	72.7	9.7	10
+15	75.3	10.3	6	71.5	11.1	4
+30	79.1	6.1	9	72.3	8.0	8
+60	81.6	16.2	5	70.7	5.2	6
+105	72.7	4.3	6	68.0	4.2	6
+150	82.8	7.4	5	71.0	9.0	4
+210	72.3	4.1	6	67.3	7.8	6
+270	71.1	6.3	7	68.8	7.9	6

TABLE2. Systolic and diastolic blood pressure averaged across subjects. (Data for Figure 2.)

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	0.0	0.0	9	0.0	0.0	10
+15	5.0	8.7	5	0.0	0.0	4
+30	9.8	9.1	8	0.0	0.0	8
+60	11.3	8.5	4	0.0	0.0	6
+105	11.7	12.1	6	0.0	0.0	6
+150	11.7	7.6	3	0.0	0.0	4
+210	1.0	2.2	5	0.0	0.0	6
+270	0.0	0.0	5	0.0	0.0	6

TABLE3. Self-rating of "highness" averaged across subjects. (Data for Figure 3.)

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	10.0	2.7	9	9.2	2.6	10
+30	8.7	1.9	10	9.9	2.5	10
+120	8.7	2.5	10	10.2	2.9	10
+240	8.4	2.4	10	10.0	2.8	10

TABLE 4.Accommmodative amplitude averaged across subjects. (Data for Figure 4).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	3.32	.16	6	3.31	.11	5
+30	2.89	.12	6	3.25	.07	6
+120	3.07	.09	6	3.40	.04	5
+240	3.23	.07	6	3.51	.09	5
PRE	1.75	.07	6	1.70	.05	5
+30	1.55	.05	6	1.32	.09	6
+120	1.53	.05	6	1.86	.07	5
+240	1.64	.07	6	1.71	.05	5
PRE	-.006	.045	6	.033	.056	5
+30	+.017	.048	6	.060	.032	6
+120	-.014	.039	6	.001	.033	5
+240	-.009	.047	6	.012	.028	5

TABLE 5. Dynamic accommodation task. Averaged response to stimuli of 0, 2, and 4 diopters averaged across subjects. (Data for Figure 5).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	-0.2	0.8	10	-0.3	0.7	10
+30	-0.7	1.3	10	-0.2	0.6	10
+120	-0.5	1.3	10	-0.3	0.7	10
+240	+0.2	.6	10	-0.6	1.1	10
PRE	0.0	0.0	10	-0.4	1.3	10
+30	0.0	0.0	10	-0.2	0.4	10
+120	0.0	0.0	10	0.0	0.0	10
+240	0.0	0.0	10	-0.1	0.3	10

TABLE 6. Phoria at 0.4 meters (top) and at 3 meters (bottom) averaged across subjects. (Data for Figure 6).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	5.42	.88	10	5.55	.76	9
+30	6.21	.66	10	5.19	.60	9
+120	6.78	.69	10	5.46	.44	9
+240	6.80	.62	9	5.42	.80	9
PRE	4.19	.56	10	4.26	.60	9
+30	4.91	.53	10	3.94	.41	9
+120	5.49	.80	10	4.04	.28	9
+240	5.52	.73	9	3.98	.56	9

TABLE 7. Pupil diameter during pre-stimulus (top) and stimulus (bottom) conditions averaged across subjects. (Data for Figure 7).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	97.0	5.6	10	97.6	4.3	9
+30	97.8	3.6	10	98.6	7.9	9
+120	97.9	4.4	10	96.5	4.5	9
+240	96.6	5.0	9	96.2	7.7	9
PRE	77.8	7.1	10	76.9	5.4	9
+30	79.4	5.7	10	76.2	4.6	9
+120	80.9	5.9	10	74.3	5.7	9
+240	81.0	6.5	9	73.8	5.4	9

TABLE 8. Percent change in pupil diameter during redilation (top) and contraction (bottom) averaged across subjects. (Data for Figure 8).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	100	5.4	9	100.4	6.2	9
+30	101.2	4.6	9	100.1	4.1	9
+120	100	6.5	9	100.5	4.5	10
+240	101.1	5.3	9	101.3	3.3	10

TABLE 9. Static visual acuity averaged across subjects. (Data for Figure 9).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	1.04	.80	9	1.07	.64	9
+30	.86	.68	10	.97	.67	10
+120	.90	.71	10	.94	.66	10
+240	.89	.69	9	1.02	.70	10

TABLE 10. Sphere power to blur acuity to 10/15 averaged across subjects. (Data for Figure 10).

	ATROPINE			PLACEBO		
FREQUENCY	MEAN	S.D.	N	MEAN	S.D.	N
1	.46	.03	8	.48	.02	9
3	.48	.02	9	.48	.02	9
5	.45	.02	9	.45	.02	9
10	.36	.01	9	.35	.03	9
20	.26	.02	9	.25	.02	9
1	.46	.04	9	.48	.02	10
3	.47	.03	9	.49	.02	10
5	.43	.02	9	.45	.02	10
10	.34	.03	9	.36	.03	10
20	.24	.02	9	.27	.03	10

TABLE 11. Contrast sensitivity function for the pre-drug session (top) & 240 minutes after injection (bottom) averaged across subjects. (Data for Figure 11).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	11.6	7.4	9	10.3	4.9	8
+30	13.8	9.3	6	7.5	4.3	7
+120	12.5	3.9	6	11.1	4.7	8
+240	13.1	6.4	6	6.6	2.0	8

TABLE 12. Glare recovery time constant averaged across subjects. (Data for Figure 12).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	15.0	3.8	9	15.1	5.3	10
+30	14.1	3.9	10	14.9	4.8	10
+120	13.5	3.3	10	13.9	4.1	10
+240	12.9	3.3	10	13.9	3.4	10

TABLE 13. Intraocular pressure (AO NCT) averaged across subjects. (Data for Figure 13).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	236	33	10	279	57	10
+30	254	40	10	279	66	10
+120	249	32	10	247	49	10
+240	267	43	8	248	37	10
PRE	248	25	10	239	60	10
+30	239	34	10	226	56	10
+120	241	37	10	273	50	10
+240	262	56	8	276	58	10

TABLE 14. Saccadic latency (top) for ten degree stimulus movements and average velocity (bottom) averaged across subjects. (Data for Figure 14).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	12.7	4.2	10	13.2	4.6	8
+30	12.8	7.2	10	11.4	3.4	8
+120	12.8	3.5	10	11.3	3.9	8
+240	10.3	3.0	10	12.2	5.9	8
PRE	13.6	3.4	10	14.2	5.5	8
+30	14.5	4.3	10	14.7	8.9	8
+120	13.1	5.0	10	14.6	6.7	8
+240	13.1	4.5	10	16.4	8.6	8

TABLE 15. Lateral postural stability with eyes open (top) and closed (bottom) averaged across subjects. (Data for Figure 15).

TABLE 16. Subject questionnaire and vital signs record. (see Figure 16).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	80.3	6.5	6	76.5	4.9	6
+90	93.3	15.9	6	73.3	8.1	6
+270	75.7	7.8	6	71.0	7.8	6

TABLE 17. Pulse rate averaged across subjects. (Data for Figure 17).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	1.0	0.0	5	1.0	0.0	4
+90	2.0	0.9	6	1.2	0.4	5
+270	1.8	1.1	5	1.0	0.0	5
PRE	2.6	1.1	5	2.5	1.0	4
+90	4.0	1.3	6	2.2	1.1	5
+270	3.2	1.3	5	2.8	1.1	5

TABLE 18. Self-rating of "highness" (top) and dryness of mouth (bottom) averaged across subjects. 1= normal & 5= very high/very dry. (Data for Figure 18).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	3.0	0.0	5	3.0	0.0	4
+90	2.5	0.5	6	2.8	0.4	5
+270	2.4	0.5	5	3.0	0.0	5
PRE	3.0	0.0	5	3.0	0.0	4
+90	2.7	0.5	6	3.4	0.9	5
+270	2.4	0.5	5	2.4	0.9	5

TABLE 19. Self-rating of coordination (top) and fatigue (bottom) averaged across subjects. 1= worse, 3= normal, & 5= better. (Data for Figure 19).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	2.36	.89	6	2.60	1.59	6
+90	2.26	.93	6	2.52	1.54	6
+270	2.60	1.66	6	2.52	1.57	6
PRE	2.50	.78	6	2.16	.34	6
+90	2.13	.45	6	2.09	.38	6
+270	2.57	.90	6	2.18	.49	6

TABLE 20. Median of twenty response times for positive accommodation (top) and negative accommodation (bottom) averaged across subjects. (Data for Figure 20).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	1.16	.69	6	1.69	2.53	6
+90	1.06	1.21	6	.75	.84	6
+270	2.40	3.86	6	.61	.57	6

TABLE 21.Difference in response times for high & low contrast targets for the positive accommodation task averaged across subjects. (Data for Figure 21).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	3.71	1.40	6	3.64	1.46	6
+90	3.32	1.31	6	3.12	.83	6
+270	3.61	1.57	6	2.76	.92	6

TABLE 22. Median visual search response time averaged across subjects. (Data for Figure 22).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	12.77	6.00	6	12.33	5.61	6
+90	12.77	7.69	6	8.00	3.29	6
+270	9.77	6.38	6	8.50	5.61	6

TABLE 23. Number of identification errors during visual search task averaged across subjects. (Data for Figure 23).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	28.11	3.65	6	26.56	7.55	6
+90	26.48	6.34	6	25.50	2.83	6
+270	24.34	6.70	6	26.11	4.32	6
PRE	25.97	2.85	6	25.45	5.45	6
+90	25.02	6.39	6	23.45	4.89	6
+270	23.44	4.91	6	23.39	4.50	6

TABLE 24. Visual search identification accuracy in the X-axis (top) and Y-axis (bottom) averaged across subjects. (Data for Figure 24).

	ATROPINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	3.0	0.0	5	3.0	0.0	4
+90	2.3	0.5	6	3.0	0.7	5
+270	2.4	0.5	5	2.6	0.5	5
PRE	3.0	0.0	5	3.0	0.0	4
+90	2.8	0.4	6	3.4	0.9	5
+270	3.0	0.0	5	3.0	0.0	5

TABLE 25.Self-rating of concentration (top) and confusion (bottom) averaged across subjects. 1= worse, 3= normal, & 5= better. (Data for Figure 25).

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